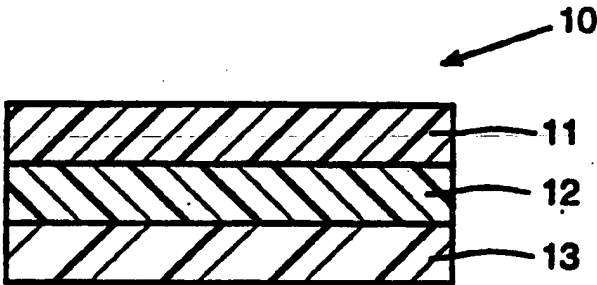


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>5</sup> :</b> <b>A61K 9/14, 9/70</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 94/07468</b> <b>(43) International Publication Date:</b> 14 April 1994 (14.04.94)
<b>(21) International Application Number:</b> PCT/US93/09510 <b>(22) International Filing Date:</b> 5 October 1993 (05.10.93)  <b>(30) Priority data:</b> 07/956,635      5 October 1992 (05.10.92)      US 08/056,076      30 April 1993 (30.04.93)      US  <b>(71) Applicant:</b> CYGNUS THERAPEUTIC SYSTEMS [US/ US]; 400 Penobscot Drive, Redwood City, CA 94063 (US).  <b>(72) Inventors:</b> HSU, Tsung-Min ; Nan-Hai Road 103-7 1F, Taipei (TW). CHEN, Tung, Fen ; 1674 Hollenbeck Ave- nue, #20, Sunnyvale, CA 94087 (US).		<b>(74) Agents:</b> CIOTTI, Thomas, E. et al.; Morrison & Foerster, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).  <b>(81) Designated States:</b> AU, CA, FI, JP, KR, NO, NZ, Euro- pean patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> TWO-PHASE MATRIX FOR SUSTAINED RELEASE DRUG DELIVERY DEVICE  <div data-bbox="526 1304 1118 1587"></div> <b>(57) Abstract</b> <p>A two-phase hydrophilic drug-containing matrix for use in transdermal drug delivery patches (10) in which one phase is a continuous hydrophobic polymer phase which optionally includes a hydrophobic solvent that acts as a skin permeation enhancer and the other phase is a dispersed particulate hydrated inorganic silicate in whose absorbed aqueous phase the drug is dissolved. A simple transdermal patch structure (10) contains a backing layer (11), a matrix layer (12) and a release liner layer (13) as components.</p>		

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LJ	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

-1-

5                    TWO-PHASE MATRIX FOR SUSTAINED RELEASE  
                    DRUG DELIVERY DEVICE

Description

10

Technical Field

                    The present invention is in the field of  
                    controlled or sustained release drug formulations and  
                    relates specifically to a two-phase drug-containing  
15                    matrix that may be used as a component in a transdermal  
                    patch.

Background

                    In general there are two types of transdermal  
20                    patch designs: a "reservoir" type and a "matrix" type.  
                    In the reservoir type the drug, typically in fluid form,  
                    is contained within a walled reservoir whose basal  
                    surface is permeable to the drug. In the matrix type the  
                    drug is dispersed in a polymer layer, typically an  
25                    adhesive, and the matrix directly contacts the skin.  
                    Both types of device also typically include a backing  
                    layer and an inner release liner layer that is removed  
                    prior to use.

                    The present invention concerns a matrix-type  
30                    device in which the matrix includes a particulate  
                    hydrated hydrophilic material that contains the drug and  
                    defines at least a portion of the basal surface area of  
                    the matrix.

35

-2-

Several prior patents describe two-phase matrixes used in transdermal drug devices, but all are distinct from the matrixes of the present invention.

U.S. 4,668,232 describes a matrix for a  
5 transdermal patch which comprises a water-insoluble adhesive, drug that is soluble in the adhesive, and a water-swellaable polymer. The inclusion of the water-swellaable polymer is alleged to increase the release rate of drug from the matrix.

10 EPA 0391172 describes a transdermal patch having a matrix composed of a water-insoluble material that contains islands of a solid solution of drug in a water-soluble/swellaable polymer and an underlayer that controls the amount of water vapor passing from the skin  
15 to the matrix. The matrix is said to be activated by water vapor from the skin.

U.S. 4,559,222 describes a transdermal matrix-type patch in which the matrix is composed of a mixture of mineral oil, polyisobutylene (an adhesive), and  
20 colloidal silicon dioxide. The addition of the silicon dioxide allegedly affects the flow characteristics of the mineral oil-polyisobutylene mix.

U.S. 5,071,657 describes a transdermal patch matrix of a drug-containing gel that is dispersed in a  
25 cross-linked silicone polymer. This matrix is apparently not adhesive as the patent teaches the use of a separate peripheral adhesive layer to affix the patch to the skin.

EPA 0452837A2 describes an adhesive matrix composed of a hydrophobic polymer, a hydrophilic drug, a  
30 hydrophilic swellaable polymer, water, and a permeation enhancer. The water is said to act as a solubilizer for the drug and the hydrophilic swellaable polymer acts to facilitate the mixing of the ingredients and improve the stability of the matrix.

35

-3-

The invention provides a novel matrix composed of a continuous hydrophobic domain and a dispersed particulate hydrated silicate domain which may be used to administer hydrophilic drugs in a sustained manner. The invention permits hydrophilic drugs to be effectively dispersed in a hydrophobic phase, maintains separation of the drug from the hydrophobic phase so that potential interaction between the two is reduced, and provides enhanced release of hydrophilic drugs from matrixes composed of a continuous hydrophobic domain.

#### Disclosure of the Invention

One aspect of the invention is a sustained-release drug formulation comprising a matrix of:

- (a) a continuous hydrophobic polymer phase;
- (b) a particulate phase dispersed in the continuous polymer phase comprised of:
  - (i) a hydrated inorganic silicate;
  - (ii) a water-solubilizable drug at least partly dissolved in the aqueous phase of (i); and
- (c) a dispersing agent for dispersing (b) in (a),

wherein the particulate phase defines at least a portion of the surface area of the matrix and provides a diffusion pathway for the drug in the matrix.

Another aspect of the invention is a transdermal patch comprising a laminated composite of:

- (a) a backing layer; and
  - (b) a layer of the above-described matrix
- wherein the continuous hydrophobic polymer phase is a pressure sensitive adhesive.

Still another aspect of the invention is a matrix of

- (a) a continuous hydrophobic polymer phase;

-4-

(b) a particulate phase dispersed in the continuous polymer phase comprised of:

a hydrated inorganic silicate and an aqueous phase; and

5 (c) a dispersing agent for dispersing (b) in (a)

wherein the particulate phase defines at least a portion of the surface area of the matrix and provides a diffusion pathway in the matrix for an active ingredient  
10 that can be water-solubilized.

Still another aspect of the invention is a process for preparing the above described sustained release drug formulation which comprises:

(1) solubilizing on water-solubilizable drug  
15 in a liquid aqueous medium;

(2) combining the solubilized drug with the aqueous medium with a hydrated inorganic silicate source;

(3) dispersing the product of step (2) with a hydrophobic polymer and optionally a surfactant to form a  
20 dispersion; and optionally

(4) applying the dispersion of step (3) to a backing; and

(5) removing excess liquid aqueous medium.

#### 25 Brief Description of the Drawing

The drawing is a cross-sectional view (not to scale) of a transdermal patch that includes the matrix formulation of the invention.

#### 30 Modes for Carrying Out the Invention

As used herein with respect to the continuous phase, the term "hydrophobic" intends that the material is less than 20% by weight soluble in water at 32°C, over  
24 hr.

35

-5-

As used herein, the term "substantially insoluble" intends a solubility of less than about 1% by weight, more usually less than about 0.5% by weight.

As used herein the term "continuous" intends a phase that is interconnected and not separated into distinct domains, segments, or particles.

As used herein with respect to the drug, the terms "hydrophilic" and "water soluble" are intended to be synonymous and to denote that the drug has a water solubility of at least about 0.1 mg/L, preferably at least about 1 mg/L at 32°C.

The term "hydrated" intends that the dispersed particulate material comprises all or a portion of its total absorptive capacity of absorbed aqueous phase (i.e. water and/or other polar solvent).

The term "sustained release" intends a formulation that is capable of releasing a therapeutically effective amount of drug over a time period of one to seven days.

The material that constitutes the continuous phase or hydrophobic domain of the matrix is a hydrophobic polymer that is capable of being mixed with the other components of the matrix and formed into a layer or film. When the matrix is used as the drug-containing matrix of a transdermal patch, the hydrophobic polymer preferably has pressure-sensitive adhesive properties that permit the matrix to adhere to living human skin for a sustained period of time, i.e., usually at least about one to seven days. Because the polymer is hydrophobic, the drug is substantially insoluble and immiscible in the polymer. Specific examples of polymers that may be used as the continuous hydrophobic phase of the matrix are polysiloxanes, polyisobutylene, solvent-based hydrophobic polyacrylates, polyurethanes, plasticized ethylene-vinyl acetate copolymers, low

-6-

molecular weight polyether block amide copolymers, styrene-butadiene polymers, and vinyl acetate-based adhesives. The hydrophobic polymer will normally constitute about 30% to 95% by weight of the matrix, more  
5 usually 40% to 60% by weight. Other hydrophobic materials such as solvents or permeation enhancers may be included in the hydrophobic domain of the matrix. Examples of such materials are fatty acids (oleic and stearic acid), isopropyl myristate (IPM), fatty acid  
10 esters (e.g., propylene glycol monolaurate, polyethylene glycol monolaurate (PEGML), methyl oleate, oleyl oleate), fatty alcohols (e.g., oleyl alcohol), and terpenoids (limonene, menthol,  $\beta$ -pinene, and geraniol).

The dispersed inorganic silicate is in the form  
15 of particles that are typically in the non-colloidal size range of 0.001 to 0.1 mm (largest dimension), more usually 0.01 to 0.05 mm. In its hydrated form the material will normally contain about 15% to 600% of its own weight in absorbed water, more usually 100% to 500%  
20 of its own weight in water (measured at 25°C). Other hydrophilic polar solvents such as ethanol, propylene glycol, low molecular weight (200 to 400 mw) polyethylene glycol, isopropyl alcohol, N-butanediol, m-pyrol and benzyl alcohol may be substituted for water or included  
25 in the hydrophilic domain of the matrix. These solvents may be used to increase the solubility of the drug in the absorbed aqueous phase. The hydrated silicate should be stable in the presence of the other components of the matrix and not adversely interact therewith. The loading  
30 and particle size of the silicate phase should be such that diffusion pathways defined by the aqueous component of the phase be available for the drug to diffuse from within the matrix to the surface of the matrix. In other words, there is substantial particle-to-particle contact  
35 in the dispersed phase. The unhydrated silicate will

-7-

normally constitute about 2% to 20% by weight of the matrix, more usually 4% to 10% by weight. The silicate may be synthetic, purified, or in a natural form (e.g., clay or talcum). Calcium, magnesium and aluminum  
5 silicates and mixtures thereof are preferred. Calcium silicates which have high water and oil absorptions (i.e., >400% by weight) are particularly preferred.

The particulate hydrated silicate is dispersed uniformly throughout the matrix and will define a portion  
10 of the surface area of the matrix. That portion should be sufficiently great to provide the desired flux of drug from the matrix. When the matrix is adhesive and is intended to adhere to skin, the portion should not be so great as to cause the matrix to lack sufficient  
15 adhesiveness to the skin. Usually the portion of the surface area defined by the hydrated silicate will be in the range of about 0.1 to 20%, more usually 0.5 to 10%.

The drugs that may be used in the matrixes of this invention are hydrophilic and are dissolved in the  
20 aqueous component of the hydrated silicate. Correlatively, the drug is substantially insoluble in the hydrophobic polymer component of the matrix and hence no significant amount of drug is dissolved in that polymer. The amount of drug present in the matrix will depend upon  
25 the amount of aqueous component present in the matrix and the solubility of the drug in that component. It will normally constitute 1% to 20% by weight of the matrix. The concentration of drug in the aqueous component of the matrix will be at or below saturation.

30 Examples of hydrophilic drugs that may be used in the matrixes of the invention are, without limitation, nicardipine hydrochloride, methylsalicylic acid, nitroglycerine, hydrophilic serotonin 5-HT<sub>3</sub> receptor antagonists such as ondansetron (sold under the brand  
35 nam ZOFTRAN) and granisetron, aminotetralins such as

-8-

S(-)-2-(N-propyl-N-2-thienylethylamine)-5-hydroxytetralin, and those drugs disclosed in pages 4-6 of European Patent Application Pub. No. 0452837A2 (Application No. 91105933.5).

5           The matrix also contains a dispersing agent which aids in maintaining the particulate phase dispersed in the continuous phase. Anionic, cationic, amphoteric or nonionic dispersing agents may be used. Preferably, the dispersing agent is a nonionic surfactant. Examples  
10 of such dispersing agents are polyethylene-polyoxypropylene glycol copolymers (sold under the Pluronic trademark), polyoxyethylene sorbitan esters (sold under the Tween trademark) such as polyoxyethylene sorbitan monolaurate, polyoxyethylene sorbitan  
15 monopalmitate, polyoxyethylene sorbitan monostearate, and polyoxyethylene sorbitan monooleates, and sorbitan esters (sold under the Span trademark) such as sorbitan monolaurate, sorbitan monostearate, and sorbitan monooleate. The dispersing agent will normally  
20 constitute 0.5% to 10% by weight of the matrix, more usually 3% to 6% by weight of the matrix.

          The matrixes of the invention may be prepared by dissolving the drug in water and optionally other hydrophilic polar solvents and contacting the hydrophilic  
25 particulate material with the resulting solution to permit the aqueous solution to be absorbed by the particulate material. This mixture will typically have the texture of a paste. The hydrophobic components of the matrix and the dispersing agent, preferably in  
30 admixture, are added to the paste with vigorous mixing to form a viscous dispersion. This dispersion may be formed into appropriate shapes and excess solvent removed therefrom. When the matrix is to be part of a transdermal or transbuccal patch, the hydrophobic domain  
35 will normally possess pressure sensitive adhesive

-9-

properties and the matrix will be cast as a layer or film onto a backing layer. Materials for forming backing layers are well-known in the transdermal patch art and are amply exemplified in the transdermal patch patent literature. Typically, the patch will include a basal release liner layer that is removed prior to use to expose the matrix. A simple and typical transdermal patch structure, generally designated 10, is shown in Figure 1 wherein 11 designates the backing layer, 12 the matrix layer, and 13 the release liner layer.

In addition to being useful as a component in transdermal or buccal patches, the matrixes of the invention may be formed into tablets for oral administration of the drugs or into inserts or implants for releasing drug into body cavities or within tissues.

The invention is further illustrated by the following examples. These examples are not intended to limit the invention in any manner. Unless indicated otherwise, percentages are by weight.

#### Example 1

##### Drug Formulation

A matrix composed of 4% of the hydrophilic drug (R)-(-)-N-(1-Methyl-4-(3-methylbenzyl)hexahydro-1H-1, 4-diazepin-6-yl)-1H-indazole-3-carboxamide dihydrochloride, 10% propylene glycol monolaurate (PGML), 20% propylene glycol (PG), 20% distilled water, 7% calcium silicate powder (Micro-Cel E) and 2% nonionic surfactant (Pluronic L-121) in a polydimethylsiloxane adhesive (Dow Corning Silicone 2920) was prepared by dissolving the drug in the PG and water, mixing the solution with the calcium silicate powder to form a paste, and vigorously mixing the paste with a mixture of the adhesive, PGML and surfactant to form a viscous dispersion.

35

-10-

Th dispersion was cast nto a 25 micron thick polyester film (silicone-coated M linex 329 from ICI) to a thickness of 250 microns using a Gardener knife and the composite was dried in an oven at 70°C for 30 min to  
5 remove excess solvent. After cooling, the composite was laminated onto a 75 micron thick polyester backing (3M, 1022).

For comparison purposes, the drug was formulated in various single phase matrixes and formed  
10 into laminated composites as above.

#### Skin Flux Testing

Human epidermis was obtained from the full thickness skin which was frozen prior to being separated.  
15 Separation of the skin at the dermal/epidermal junction was achieved by immersing the skin in water at 60°C for two minutes, and then teasing off the dermis. The heat separated epidermis was stored at 20°C pending use.

Vertically aligned diffusion cells with a  
20 diffusional area of 0.71 cm<sup>2</sup> and a receiver fluid of 8.0 ml were used. A pH 5.0 phosphate buffer was chosen as a receiver fluid to ensure an infinite sink condition being maintained because this buffer solution exhibited reasonable solubility for the drug. Skin flux studies  
25 were conducted for a period of 30 hours.

A 1 3/4 cm diameter section of separated epidermis was punched and mounted in the diffusion cell with the stratum corneum facing the donor compartment. The laminated composites were punched out in 1 3/4 cm  
30 diameter circles. After peeling from the releasing side of polyester film, the drug matrix was then mounted between two compartments of the diffusion cell.

After a designated time period has elapsed, a 1 ml sample was taken from the receiver compartment with a  
35 micr pipette from a given diffusi n cell. An equivalent

-11-

amount of receiver solution was added in the receiver chamber to maintain a constant volume. Dilution of the receiver medium was taken into account when processing the permeation data. Table 1 below reports the results of these skin flux tests. Flux is reported as the average flux over 30 hrs.

Table 1

	<u>Formulation</u>	<u>Skin Flux (<math>\mu\text{g}/\text{cm}^2/\text{hr}</math>)</u>
10	<u>Single Phase Comparisons</u>	
	2% drug in Silicone 2920 adhesive	0
	2% drug in Morstik 607 <sup>1</sup> adhesive	0
	2% drug in Gelva 788 <sup>2</sup> adhesive	0
15	2% drug, 10% PGML, 10% m-Pyrol in Silicone 2920 adhesive	0.5
	2% drug, 10% PGML, 10% m-Pyrol in Morstik 607 adhesive	0
20	4% drug, 20% PGML, 20% m-Pyrol in Kraton 36-6172 <sup>3</sup> adhesive	0.8
	<u>Two-Phase</u>	
	4% drug, 10% PGML, 20% PG 20% Dist. water, 7% Micro-Cel E 2% Pluronic L-121 in Silicone 2920 adhesive	17.1
25	1 Morstik 607 is an acrylate adhesive. 2 Gelva 788 is an acrylate adhesive. 3 Kraton 36-6172 is a styrene-butadiene copolymer adhesive.	

30 As shown in Table 1, the skin flux of the drug from the two-phase matrix of the invention was vastly greater than the skin flux from any of the comparison single-phase matrixes tested.

35

-12-

Examples 2-6

These examples illustrate variations of the two-phase matrix formulation of Example 1 in which the proportions of the components differ. These matrixes were prepared and tested as in Example 1. Table 2 below provides details of the compositions of these matrixes and the results of the skin flux tests on them.

Table 2

Example No.	Formulation	Skin Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )
2	4% drug, 10% PGML, 30% PG 20% Dist. water, 7% Micro- Cel E, 3% Pluronic L-121 in Silicone 2920	15.7
3	4% drug, 15% PGML, 20% PG, 10% Dist. water, 7% Micro- Cel E, 3% Pluronic L-121 in Silicone 2920	9.1
4	6% drug, 6% PGML, 30% PG, 20% Dist. water, 7% Micro- Cel E, 3% Pluronic L-121 in Silicone 2920	20.4
5	6% drug, 6% PGML, 50% PG, 20% Dist. water, 8% Micro- Cel E, 3% Pluronic L-121 in Silicone 2920	23.9
6	6% drug, 12% PGML, 30% PG, 26% Dist. water, 8% Micro- Cel E, 3% Pluronic L-121 in Silicone 2920	25.7

Examples 7-8

These examples illustrate two-phase matrix formulations similar to those of Examples of 1-6 but using a different silicone adhesive (Dow Corning 4201). The matrixes were prepared and tested as in Example 1. Table 3 below provides details of the compositions of these matrixes and the results of the skin flux tests on them.

-13-

Table 3

Example No.	Formulation	Skin Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )
5	7 4% drug, 15% PGML, 20% PG 10% Dist. water, 7% Micro- Cel E, 3% Pluronic L-121 in Silicone 4201	12.0
10	8 2% drug, 5% PGML, 20% PG, 15% Dist. water, 2% Micro- Cel E, 3% Tween in Silicone 4201	5.4

Examples 9-12

These examples illustrate matrixes similar to that of Example 1 in which the hydrophobic solvent was different than PGML. The matrix formulation consisted of 4% drug, 20% PG, 15% distilled water, 7% calcium silicate, 2% Tween 80 surfactant and the indicated % of hydrophobic solvent in polydimethylsiloxane adhesive (Dow Corning 4201). The matrixes were prepared and tested as in Example 1. Table 4 below provides details on the composition and amount of the hydrophobic solvent and the results of the skin flux tests.

Table 4

Example No.	Hydrophobic Solvent	Skin Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )
9	12% PEGML, 3% IPM	6.4
10	10% Oleyl Oleate	2.1
11	10% Oleic Acid	2.0
30	12% Oleyl Alcohol	9.6

Examples 13-14

These examples illustrate matrixes similar to that of Example 1 in which the silicates other than

-14-

Micro-Cel E were used. These matrixes were prepared and tested as in Example 1. Table 5 below provides details of the compositions of these matrixes and the results of the skin flux tests.

5

Table 5

Example No.	Formulation	Skin Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )
10	13      2% Drug, 5% Oleyl Alcohol, 20% PG, 15% Dist. water, 1% Talc, 3% Tween 80 in Silicone 4201	2.1
15	14      2% Drug, 5% Oleyl Alcohol, 20% PG, 15% Dist. water, 1% Kaolin, 3% Tween 80 in. Silicone 4201	1.2

Example 15

S(-)-2-(N-propyl-N-2-thienylethylamine)-5-hydroxytetralin is a selective  $D_2$  agonist for treating Parkinson's disease. The effective dose for treating Parkinson's disease is estimated to be in the range of about 1 to 3  $\mu\text{g}/\text{kg}/\text{hr}$ . Accordingly, for transdermal administration, the target flux of this drug (based on a 20  $\text{cm}^2$  delivery area) is estimated to be in the range of approximately 3-10  $\mu\text{g}/\text{cm}^2/\text{hr}$ .

Skin flux studies of this drug from various liquid formulations showed that fluxes at or above the effective range could be achieved from saturated solutions of the drug in pH 6.0 buffer or PGML. Similar studies of the flux of this drug from simple matrix systems in which the drug and PGML were formulated in various adhesives (silicone, polyisobutylene, or Morstik 607 acrylate) did not provide effective flux levels.

In contrast a series of five two-phase matrix formulations of this drug were prepared in accordance

-15-

with the present invention. Table 6 below presents the composition of those matrixes and the results of the flux tests thereon.

5

Table 6

	Matrix	1	2	3	4	5	6	7	8	Skin Flux ( $\mu\text{g}/\text{cm}^2/\text{hr}$ )
10	A	2	10	5	5	10	4	3	61	6.41 $\pm$ 0.13
	B	4	10	5	5	10	4	3	59	14.2 $\pm$ 0.6
	C	4	0	5	5	10	4	6	66	8.66 $\pm$ 0.19
	D	4	5	5	5	10	4	5	62	15.5 $\pm$ 0.19
	E	4	10	5	5	10	2	3	61	13.7 $\pm$ 1.2

15

1 = Drug (%)  
 2 = PGML (%)  
 3 = Benzyl alcohol (%)  
 4 = PG (%)  
 5 = pH 6.0 phosphate buffer (%)  
 6 = Micro-Cell E (%)  
 7 = Span 60 Emulsifier (%)  
 8 = Silicone 4201 Adhesive (%)

20

As indicated, all five of the two-phase matrixes provided fluxes at or above the target level.

Example 16

25

Based on the results of Example 15, two optimized formulations of S(-)-2-(N-propyl-N-2-thienylethylamine)-5-hydroxytetralin. These formulations lacked any PGML, benzyl alcohol or PG. One contained 4% drug, 20% phosphate buffer (pH 6.0), 4% Micro-Cell E, 4% Span 60 emulsifier, and 4% silicone medical fluid 360 (Dow Corning) in silicone 4201 adhesive. The other contained 5% drug, 18% buffer, 5% Micro-Cell E, 4% Span 60 emulsifier, and 4% silicone medical fluid 360 in silicone 4201 adhesive. The flux from these formulations

30

35

-16-

was comparable to those from matrixes B, D, and E of Example 15.

5        Modifications of the above modes for carrying out the invention that are obvious to those of skill in pharmaceuticals, sustained release formulation, transdermal drug delivery, polymers, pressure sensitive adhesives, and related fields are intended to be within the scope of the following claims.

10

15

20

25

30

35

-17-

CLAIMS

1. A sustained release drug formulation comprising a matrix of:
    - 5 (a) a continuous hydrophobic polymer phase;
    - (b) a particulate phase dispersed in the continuous polymer phase comprised of:
      - (i) a hydrated inorganic silicate;
      - (ii) a water-solubilizable drug at least
      - 10 partly dissolved in the aqueous phase of (i); and
      - (c) a dispersing agent for dispersing (b) in (a),wherein the particulate phase defines at least a portion of the surface area of the matrix and provides a
  - 15 diffusion pathway for the drug in the matrix.
- 
2. The sustained release drug formulation of claim 1 wherein the drug comprises 1% to 20% by weight of the matrix, the inorganic silicate (unhydrated) comprises
  - 20 2% to 20% by weight of the matrix, and the hydrophobic polymer phase comprises 30% to about 95% by weight of the matrix.
- 
3. The sustained release drug formulation of
  - 25 claim 1 or 2 wherein the hydrated inorganic silicate contains 15% to 600% of its own weight in absorbed aqueous phase.
- 
4. The sustained release drug formulation of
  - 30 claim 2 wherein the hydrated inorganic silicate contains 100% to 500% of its own weight in absorbed aqueous phase.
- 
5. The sustained release drug formulation of claim 1 wherein the hydrated inorganic silicate is

35

-18-

calcium silicat , magnesium silicate, aluminum silicat ,  
or mixtures th re f.

5           6.    The sustained release drug formulation of  
claims 1 to 5 wherein said surface area portion  
constitutes 0.1% to 20% of the surface area of the  
matrix.

10           7.    The sustained release formulation of claim  
1 or 2 wherein the hydrophobic polymer phase includes a  
hydrophobic solvent.

15           8.    The sustained release formulation of claim  
7 wherein the hydrophobic solvent is a skin permeation  
enhancer.

20           9.    The sustained release formulation of claim  
7 or 8 wherein the hydrophobic solvent is a fatty acid, a  
fatty acid ester, a fatty alcohol, or a terpenoid.

25           10.   The sustained release drug formulation of  
claims 1 to 5 wherein the hydrated inorganic silicate  
includes an absorbed polar solvent that increases the  
solubility of the drug in water.

30           11.   The sustained release drug formulation of  
claim 10 wherein the polar solvent is ethanol, propylene  
glycol, low molecular weight polyethylene glycol,  
isopropyl alcohol, n-butanediol, m-pyrol, or benzyl  
alcohol.

35           12.   The sustained release formulation of claim  
1 or 2 wherein the drug is (R)-(-)-N-(1-Methyl-4-(3-  
methylbenzyl)hexahydro-1H-1, 4-diazepin-6-yl)-1H-  
indazol -3-carb xamid dihydr chl ride, ondans tron,

-19-

granisetron, or S(-)-2-(N-propyl-N-2-thienylethylamine)-5-hydroxytetralin.

13. The sustained release drug formulation of  
5 claims 2 to 5 wherein the hydrated inorganic silicate is calcium silicate, the hydrophobic polymer is a silicone, the formulation includes propylene glycol and propylene glycol monolaurate, and the drug is (R)-(-)-N-(1-Methyl-4-(3-methylbenzyl)hexahydro-1H-1, 4-diazepin-6-yl)-1H-  
10 indazole-3-carboxamide dihydrochloride or S(-)-2-(N-propyl-N-2-thienylethylamine)-5-hydroxytetralin.

14. A transdermal patch comprising a laminated composite of:  
15 (a) a backing layer and  
(b) a layer of the formulation of one of the preceding claims (1 to 13) wherein the continuous hydrophobic polymer phase is a pressure sensitive adhesive.

20 15. A matrix of  
(a) a continuous hydrophobic polymer phase;  
(b) a particulate phase dispersed in the continuous polymer phase comprised of:  
25 a hydrated inorganic silicate and an aqueous phase; and  
(c) a dispersing agent for dispersing (b) in (a),  
wherein the particulate phase defines at least a portion  
30 of the surface area of the matrix and provides a diffusion pathway in the matrix for an active ingredient that can be water-solubilized.

16. The use of the matrix of claim 15 in the  
35 preparation of a sustained release drug formulation.

-20-

17. A process for preparing a sustained  
release drug formulation of claims 1 to 14 which  
comprises:

- 5 (1) solubilizing a water-solubilizable drug in  
a liquid aqueous medium;
- (2) combining the solubilized drug with the  
aqueous medium with a hydratable inorganic silicate  
source;
- 10 (3) dispersing the product of step (2) with a  
hydrophobic polymer and optionally a surfactant to form a  
dispersion; and optionally
- (4) applying the dispersion of step (3) to a  
backing; and
- (5) removing excess liquid aqueous medium.

15

20

25

30

35

1 / 1

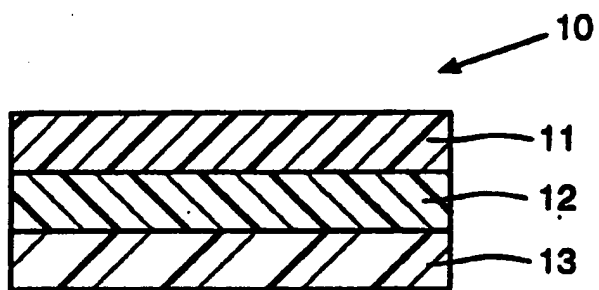


FIG. 1

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/09510

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(5) : A61K 9/14, 9/70

US CL : 424/484

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/484, 449, 486; 514/438

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,906,463 (CLEARY ET AL) 06 MARCH 1990; See entire document.	1-5,7,8,12, 15
Y	EP, A, 0 358 903 (DAINIPPON PHARMACEUTICAL CO., LTD.); 21 MARCH 1990; See page 7, line 6 and page 17, lines 40-56.	12
<u>X</u>	US, A, 5,071,645 (JOHNSON ET AL)	<u>1,5,15</u>
Y	10 DECEMBER 1991; See entire document.	2-4,7,8,12

☐ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be part of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E* earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G*	document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means		
*P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 NOVEMBER 1993	Date of mailing of the international search report 07 JAN 1994
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer ROBERT H. HARRISON Telephone No. (703) 308-2351

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/09510

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 16  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Claim 16 is directed to a "use". PCT Article 17(2)(a)(i). "Use" claims not in method terminology are not searched by this authority.
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6, 9-11, 13-14, 17  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.